EXHIBIT A

Docket No.: 085742-0487 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Customer Number: 20277
Bianca BROGMANN, et al.	:	Confirmation Number: 1884
Application No.: 10/510,674	:	Group Art Unit: 1627
Filed: May 23, 2005	:	Examiner: Samira JEAN-LOUIS

For: PHARMECEUTICAL PREPARATION CONTAINING OXYCODONE AND NALOXONE

DECLARATION UNDER 37 CFR 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Michael Hopp, hereby declare:

1. I am a German citizen and am more than twenty-one years of age.

2. I earned a Medical Degree from Johann-Wolfgang-Goethe University, Frankfurt/Germany.

3. I hold the position of Head of Medical Science Pain. A copy of my *curriculum vitae* is attached as Exhibit A.

4. I am familiar with the specification and claims of U.S. Patent Application No. 10/510,674, filed May 23, 2005 as a national phase application of international application No. PCT/EP03/03540 (filed April 4, 2003).

5. I have reviewed the Office Action mailed January 5, 2010 ("the Office Action"); WO 99/32119 ("Kaiko"); and U.S. Patent No. 3,773,955 ("Pachter").

6. In the Office Action, the Examiner states that Kaiko teaches an oral dosage form comprising an opioid agonist and an opioid antagonist in a ratio that is analgesically effective when administered but aversive in physically dependent subjects; sustained release via incorporation of a sustained release carrier into a matrix or a sustained release coating; naloxone in an amount that is equi-antagonistic to naltrexone, and naloxone doses of 0.8 mg – 24 mg; oxycodone and pharmacologically acceptable salts or esters thereof; and prior art oxycodone-naloxone compositions having a ratio of 2.5-5:1 parts by weight. The Examiner states that Kaiko does not teach a pharmaceutical preparation containing oxycodone-naloxone with the specific weight ratio of 2:1 or a preparation in the form of specific pharmaceutically acceptable and equally active free base salts.

7. In the Office Action, the Examiner states that Pachter discloses: an oral analgesic composition comprising an orally inactive dose of naloxone and an analgesic, including oxycodone; oxycodone to naloxone ratios of 2-20 parts to 1; and that the analgesic can be any of the pharmaceutically acceptable nontoxic salts.

8. According to the Examiner, it would have been obvious to administer the oxycodone-naloxone dosage in the formulation of Kaiko in a ratio of 2:1 because Pachter teaches that such a ratio provides an effective analgetic composition that negates the euphoria and physical dependence of the composition.

9. Opioids such as oxycodone provide excellent analgesia and are often first-line treatment for patients suffering from severe pain, such as cancer pain.

10. Gastrointestinal ("GI") adverse effects associated with opioid (e.g., oxycodone) administration include, for example, constipation, nausea, spasms, cramps, bloating, and abdominal pain.

11. The GI adverse effects associated with oxycodone administration are common and can be severe.

12. The frequency and/or severity of the GI side effects associated with oxycodone administration can result in patient non-compliance and undertreatment.

13. The oxycodone/naloxone ratio (2:1) claimed in the instant application overlaps the lower limit of the range of ratios disclosed in Pachter (2:1 to 20:1).

14. Kaiko does not disclose or suggest oxycodone to naloxone ratios.

15. I have been informed that a critical value in a claim can render the claim non-obvious in view of prior art that includes the value within a range of values.

16. One of ordinary skill in the art in April 2003 would have been a Ph.D. in pharmacology with two years of experience in clinical pharmacology of pain indications.

17. One of ordinary skill in the art in April 2003 having read Meissner et al., Eur J Pain, 2009:13:56-64 ("Meissner") would have understood it to teach that a 2:1 oxycodone to naloxone ratio is a critical value because this ratio provides clinically significant benefits that were not predictable to one of ordinary skill in the art in April 2003.

18. Meissner describes a multi-center, prospective, placebo-controlled, randomized, double-blind, parallel group clinical trial of male and female patients with severe, chronic pain that required opioid treatment. One hundred sixty-six patients completed the trial. Treatment group patients received oxycodone and naloxone in ratios of 1:1, 1.5:1, 2:1, 3:1, 4:1, 6:1, and 8:1.

19. Meissner shows that the patients who received the oxycodone and naloxone in a ratio of 2:1 did the best when all aspects of treatment were taken into account, i.e., reduction of pain intensity, improvement in bowel function index, occurrence of adverse effect, avoidance of diarrhea, tolerability and preference.

20. The trial described in Meissner was designed and sponsored by Mundipharma GmbH, a company associated with the instant assignee, Euro-Celtique S.A.

21. The trial described in Meissner showed that a oxycodone to naloxone ratio of 2:1 improved bowel function relative to the higher ratios, with an approximately 50% improvement over the 4:1 ratio treatment. Further, the improvement was not associated with any lessening of the effect on pain intensity relative to other ratios, nor any increase in adverse effects.

22. The trial described in Meissner showed that patients administered oxydocone/naloxone in a ratio of 1.5:1 had a 50% incidence of diarrhea compared to a 29.4% incidence in patients administered oxydocone/naloxone in a ratio of 2:1

23. Meissner stated that the trial results showed that:

> The availability of a strong opioid with an improved tolerability profile, such as a fixed 2:1 oxycodone/naloxone combination, has significant added therapeutic value, thus representing a major advance in the treatment and quality of life of patients suffering from sever chronic pain.

Meissner, p. 64.

24. In April 2003, one of ordinary skill in the art would not have predicted that a 2:1 oxycodone to naloxone ratio would provide the optimal balance between providing pain relief while minimizing opioid associated GI adverse effects.

25. I declare further that statements made in this declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 05 Jul 2010

EXHIBIT B

CURRICULUM VITAE
DR. MED. MICHAEL HOPP

Name:	Michael Hopp
Date of Birth:	27 September 1967
Place of Birth:	Rüsselsheim
Nationality:	German
Address:	Dillenburger Str. 17, 65520 Bad Camberg, Germany

EDUCATION

1988 – 1995	Human Medicine Studies at Johann-Wolfgang-Goethe-University Frankfurt
1987 – 1988	Military Service
1987	Abitur (School Qualification A-Level)

WORK EXPERIENCE

Since 06/2010	Head of Medical Science Pain Mundipharma Research GmbH & Co. KG, Limburg
01/2001 – 06/2010	European Medical Research Physician, Responsible for Planning and Performing Clinical Studies (Programs) for Medicinal Devices and Medicinal Drugs, Mundipharma Research GmbH & Co. KG, Limburg
07/1999 – 01/2001	Medical Training for Sales Force Mundipharma Vertriebsgesellschaft mbH & Co. KG
01/1999 – 06/1999	Trainee at Societät Logos (Consultant Company in Health Services)
1996 – 01/1999	Assistant Physician (General Practicioner Practice, MTK Kliniken, Bad Soden)

DOCTORATE

Development of Selective Nutrician Agar for Pseudomonas aeruginosa at Johann-Wolfgang-Goethe-Institute Frankfurt; Institute for Hygiene

SOCIETY MEMBERSHIP

Member of IASP – International Association for the Study of Pain

PUBLICATIONS

- **Hopp M**, Ruckes Ch, Friedman M, Miller J, Leyendecker P, Reimer K, Fleischer W. The combination of naloxone with prolonged release (PR) oxycodone is able to reduce opioid-induced constipation - Results of a clinical study. Deutscher Schmerzkongress, Bremen 19.-22.10.2005. Der Schmerz 19 (2005), Suppl 1, 103 (Abstract)

- Müller S, Vogt PM, Steinau HU, Bosse B, **Hopp M**, Leuner C, Fleischer W, Reimer K. Repithel: Removing the barriers to wound healing. Dermatology 212 (2006), Suppl. 1: 77-81

- Hauser J, Rossbach O, Langer S, Vogt P, Germann G, Steinau HU, Reimer K, **Hopp M**, Langer-Brauburger B, Bosse B, Homann H. Lokale Behandlung von Grad IIa Verbrennungen, Wirksamkeit und Verträglichkeit eines neuartigen hydrosomalen Wundgels im Vergleich zu Silbersulfadiazin-Creme. Unfallchirurg 110 (2007): 988-994

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- Nadstawek J, Leyendecker P, **Hopp M**, Ruckes Ch, Wirz S, Fleischer W, Reimer K. Patient assessment of a novel therapeutic approach for the treatment of severe, chronic pain. Int. J. Clin. Pract. 2008, 62, 1159-1167

- Meissner W, Leyendecker P, Mueller-Lissner, S, Nadstawek J, **Hopp M**, Ruckes Ch, Wirz S, Fleischer W, and Reimer K. Dr Meissner and colleagues reply to the Letter to the Editor from Andrew Wilcock entitled 'Prolonged-release naloxone can cause systemic opioid withdrawal'. Eur. J. Pain 2009, 13, 1002–1003

- Meissner W, Leyendecker P, Mueller-Lissner S, Nadstawek J, **Hopp M**, Ruckes Ch, Wirz S, Fleischer W, Reimer K. A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. Eur. J. Pain 2009, 13, 56-64

- Löwenstein O, Leyendecker P, **Hopp M**, Schutter U, Rogers PD, Uhl R, Bond S, Kremers W, Nichols T, Krain B, Reimer K. Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: A randomised controlled trial. Expert Opin Pharmacother 2009, 10(4), 531-543

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- Reimer K, **Hopp M**, Zenz M, Maier Ch, Holzer P, Mikus G, Bosse B, Smith K, Buschmann-Kramm C, Leyendecker P. Meeting the challenges of opioid-induced constipation in chronic pain management – A novel approach. Pharmacology 2009, 83, 10-17

- Sandner-Kiesling A, Leyendecker P, **Hopp M**, Tarau L, Lejcko J, Meissner W, Sevcik P, Hakl M, Hrib R, Uhl R, Dürr H, Reimer K. Long-term efficacy and safety of combined prolonged release oxycodone and naloxone in the management of non-cancer chronic pain. Int J Clin Pract 2010, 64(6), 763–774